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(54) Title: PROCESS FOR REGIOSELECTIVE SUBSTITUTION OF TRIFLUOROBENZOATE OR TRIFLUOROBENZONITRILE

(57) Abstract

The invention provides a process for regioselective substitution of trifluorobenzoate/trifluorobenzonitrile to afford the difluorobenzoate/difluorobenzonitrile in good yields. The resulting difluorobenzoate/difluorobenzonitrile can again be regioselectively substituted with a second nucleophile to give monofluorobenzoate/monofluorobenzonitrile also in good yields. This process is particularly useful for forming key intermediates in the synthesis of oxytocin antagonist compounds.

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BNSDOCID: <WO___9731891A1_I_>

TITLE OF INVENTION
PROCESS FOR REGIOSELECTIVE SUBSTITUTION OF TRIFLUOROBENZOATE OR TRIFLUOROBENZONITRILE

CROSS-REFERENCE TO RELATED APPLICATIONS
Not Applicable

STATEMENT REGARDING FEDERALLY-SPONSORED R&D
Not Applicable

REFERENCE TO MICROFICHE APPENDIX
Not Applicable

FIELD OF THE INVENTION
The present invention provides a process for regioselective substitution of trifluorobenzoate and/or trifluorobenzonitrile. More particularly, regioselective nucleophilic substitution of 2, 4, 5-trifluorobenzoate/trifluorobenzonitrile at the 4-position yields 2,5-difluorobenzoate/difluorobenzonitrile in high yields. Subsequent substitution of the 2,5-difluorobenzoate/difluorobenzonitrile at the 2-position provides 5-fluorobenzoate/fluorobenzonitrile in good yields.

BACKGROUND OF THE INVENTION
In the field of obstetrics, one of the most important problems is the management of preterm labor. A significant number of the pregnancies progressing past 20 weeks of gestation experience premature labor and delivery, which is a leading cause of neonatal morbidity and mortality. Despite major advances in neonatal care, retention of the fetus *in utero* is preferred in most instances.

Tocolytic (uterine-relaxing) agents that are currently in use include β_2-adrenergic agonists, magnesium sulfate and ethanol. Ritodrine, the leading β_2-adrenergic agonist, causes a number of cardiovascular and metabolic side effects in the mother, including tachycardia, increased renin secretion, hyperglycemia (and reactive hypoglycemia in the infant). Other β_2-adrenergic agonists, including

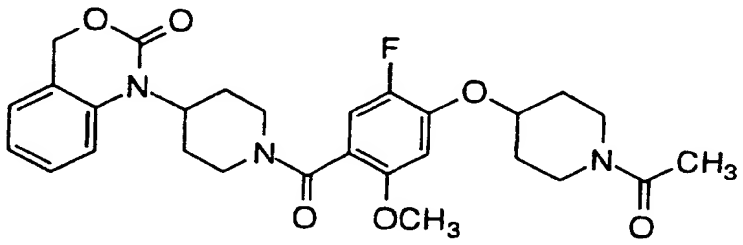
terbutaline and albuterol have side effects similar to those of ritodrine. Magnesium sulfate at plasma concentrations above the therapeutic range of 4 to 8 mg/dL can cause inhibition of cardiac conduction and neuromuscular transmission, respiratory depression and cardiac arrest, thus making this agent unsuitable when renal function is impaired. Ethanol is as effective as ritodrine in preventing premature labor, but it does not produce a corresponding reduction in the incidence of fetal respiratory distress that administration of ritodrine does.

It has been proposed that an oxytocin antagonist would be the ideal tocolytic agent. In the last few years, evidence has accumulated to strongly suggest that the hormone oxytocin may be a physiological initiator of labor in several mammalian species including humans. Oxytocin is believed to exert this effect in part by directly contracting the uterine myometrium and in part by enhancing the synthesis and release of contractile prostaglandins from the uterine endometrium/decidua. These prostaglandins may, in addition, be important in the cervical ripening process. By these mechanisms, the process of labor (term and preterm) is initiated by a heightened sensitivity of the uterus to oxytocin, resulting in part as a result of a well-documented increase in the number of oxytocin receptors in this tissue. This "up-regulation" of oxytocin receptors and enhanced uterine sensitivity appears to be due to trophic effects of rising plasma levels of estrogen towards term. By blocking oxytocin, one would block both the direct (contractile) and indirect (enhanced prostaglandin synthesis) effects of oxytocin on the uterus. An oxytocin blocker, or antagonist, would likely be more efficacious for treating preterm labor than current regimens. In addition, since oxytocin at term has major effects only on the uterus, such an oxytocin antagonizing compound would be expected to have few, if any, side effects.

It is also believed that an oxytocin antagonist compound would also be useful in the treatment of dysmenorrhea. This condition is characterized by cyclic pain associated with menses during ovulatory cycles. The pain is thought to result from uterine contractions and ischemia, probably mediated by the effect of prostaglandins produced in

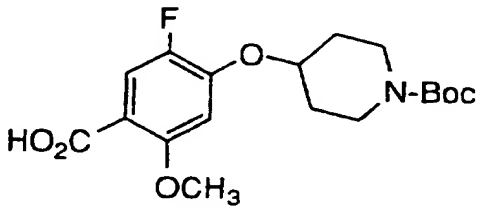
the secretory endometrium. By blocking both the direct and indirect effects of oxytocin on the uterus, a selective oxytocin antagonist can be more efficacious for treating dysmenorrhea than current regimens. An additional use for oxytocin antagonists is for stopping labor prior to cesarean delivery.

A number of potent, nonpeptide benzoxazinone oxytocin antagonists have recently been identified (see PCT International Application Publication No. WO95/02405, published January 26, 1995). Related compounds in the benzoxazinone series of oxytocin antagonists which are fluorinated on the central aromatic ring, for example Compound A shown below, are also potent oxytocin antagonists.



Compound A

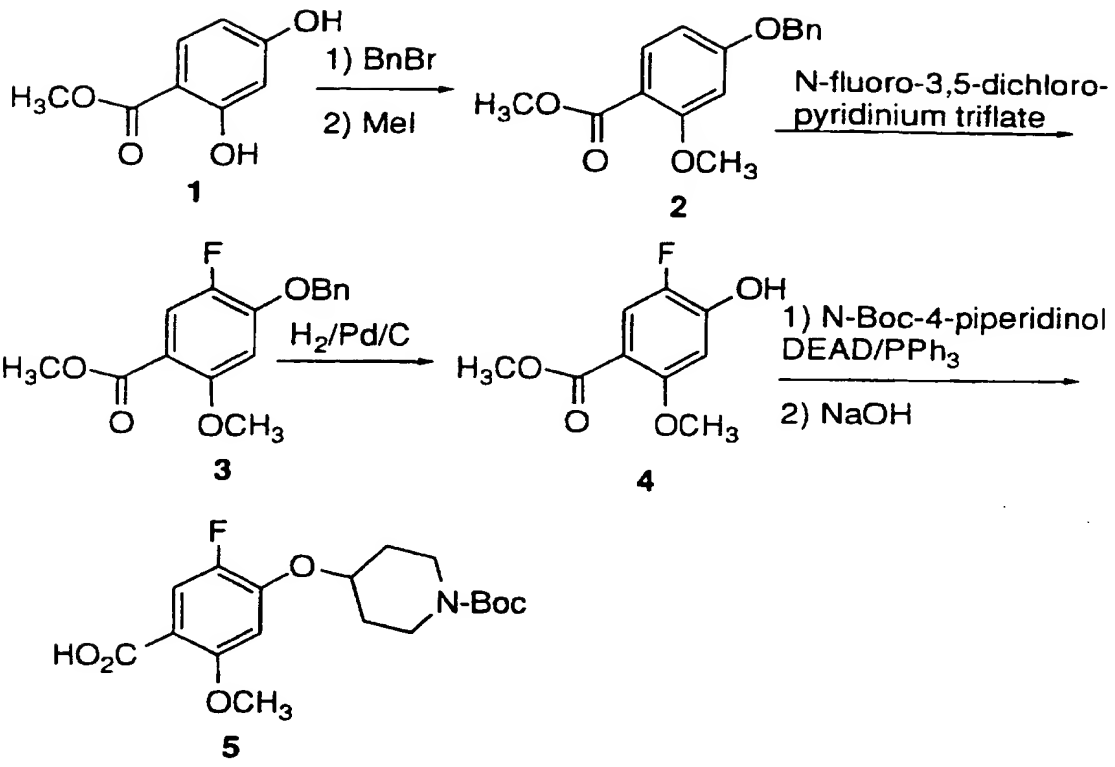
A key intermediate in the synthesis of Compound A, and other fluorine containing structurally related oxytocin antagonist compounds, is the compound **5**



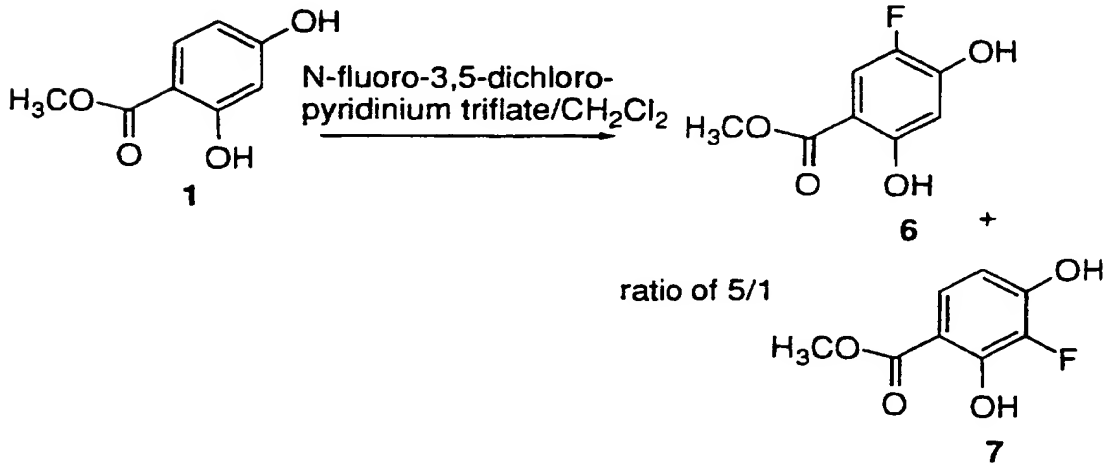
5

In the past, synthesis of intermediate **5** was accomplished by the direct fluorination of methyl-2,4-dihydroxylbenzoate or its analogs with N-fluoro-3,5-dichloropyridinium triflate which produced the desired 5-fluorobenzoate in low yields (ca. 30%), along with the undesired 3-fluorobenzoate. *See* Schemes 1 and 2 below.

SCHEME 1



SCHEME 2

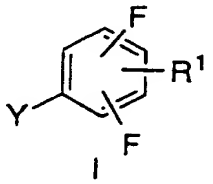


Flash chromatography was then necessary in order to remove the undesired 3-fluorobenzoate. In addition, the supply of N-fluoro-3,5-dichloropyridinium triflate is limited, and therefore, very expensive. Thus, a need remains for a more efficient synthesis of key intermediate **5**.

It has now been found that regioselective nucleophilic substitution of trifluorobenzonitrile/trifluorobenzoate provides a more efficient and less expensive route to the desired intermediate **5** in the synthesis of oxytocin antagonists useful for preterm labor, dysmenorrhea and stopping labor prior to cesarean delivery.

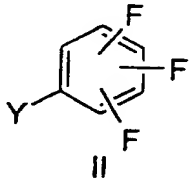
SUMMARY OF THE INVENTION

The present invention provides a process for forming a difluoro compound I



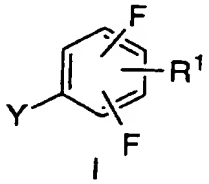
I

comprising reacting a trifluoro compound II



II

with a nucleophilic agent R^1 to obtain the difluoro compound I

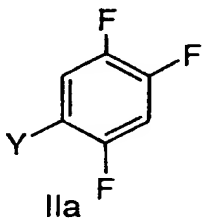


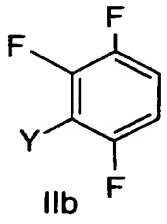
I

wherein Y is selected from CN or CO_2-C_{1-6} alkyl;
R^1 is selected from OR^3, SR^3, CN, $C{\equiv}CR^4$,

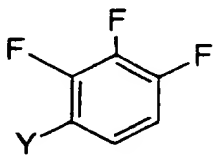
or a 4, 5, 6 or 7-membered monocyclic nitrogen containing heterocyclic ring containing one or two nitrogen atoms;
R^3 is selected from C_{1-10} alkyl, C_{3-8} cycloalkyl, phenyl-C_{1-6} alkyl, phenyl or a 4, 5, 6 or 7-membered monocyclic nitrogen containing heterocyclic ring containing one or two nitrogen atoms wherein the nitrogen containing heterocyclic ring is either unsubstituted or substituted with R^5 and R^6;
R^4 is C_{1-10} alkyl; and
R^5 and R^6 are each independently selected from CO_2R^4, COR^4 or C_{1-10} alkyl.

In one embodiment of the present invention is the process wherein the trifluoro compound is selected from

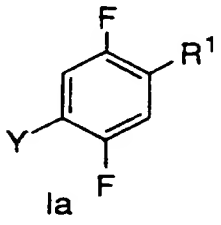

IIa

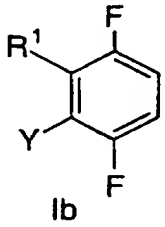

IIb

or

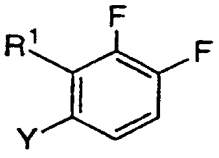

IIc

and the difluoro compound is selected from


Ia

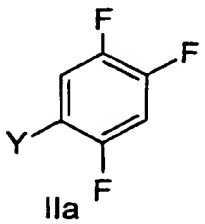

Ib

or

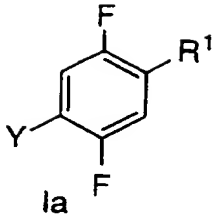

Ic

wherein all variables are as described above.

In a class of the invention is the process wherein the trifluoro compound is


IIa

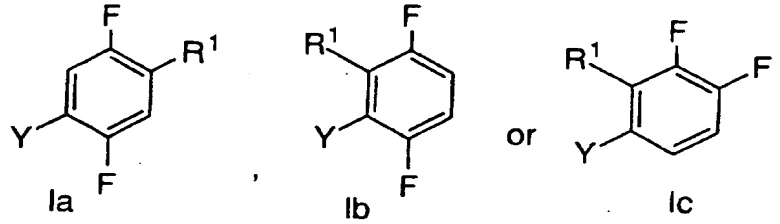
and the difluoro compound is



Ia

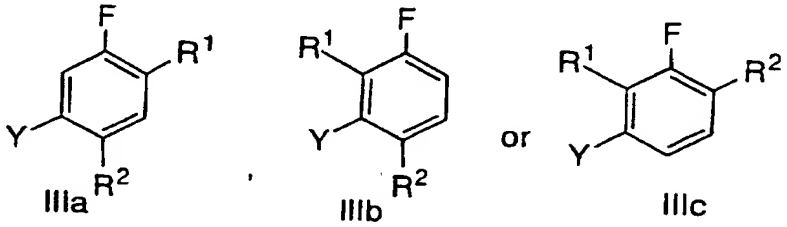
wherein all variables are as described above.

In a subclass of the invention is the process further comprising the step of reacting the difluoro compound selected from



Ia Ib Ic

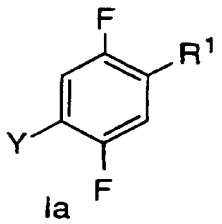
with a second nucleophilic agent R^2 to obtain a monofluoro compound selected from



IIIa IIIb IIIc

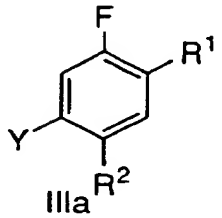
wherein R^2 is selected from OR^3, SR^3, CN, $C{\equiv}CR^4$, or a 4, 5, 6 or 7-membered monocyclic nitrogen containing heterocyclic ring containing one or two nitrogen atoms; and where all other variables are as defined above.

Illustrative of the invention is the process wherein the difluoro compound is



Ia

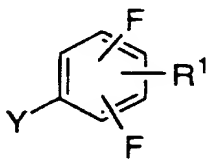
and the monofluoro compound is



IIIa

and where all variables are as described above.

Another aspect of the invention is a compound of the formula



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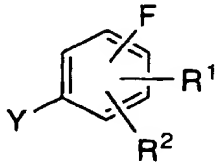
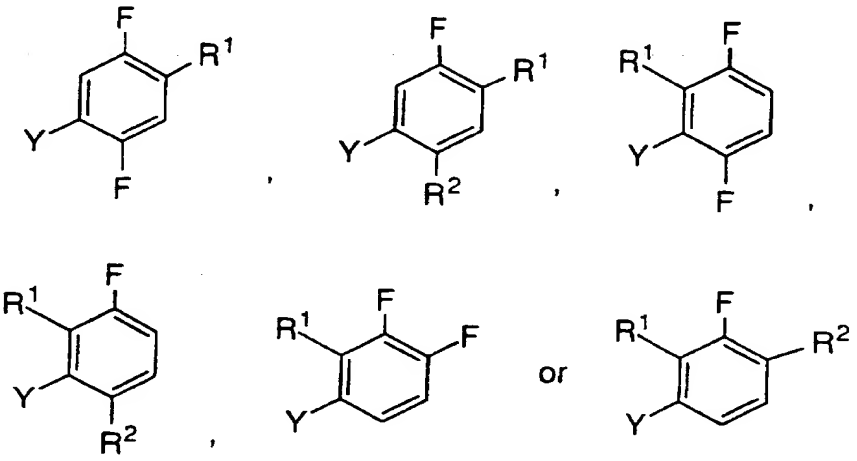


wherein Y is selected from CN, CO_2H or CO_2-C_{1-6} alkyl;
R^1 and R^2 are each independently selected from OR^3, SR^3, CN, $C{\equiv}CR^4$,
or a 4, 5, 6 or 7-membered monocyclic nitrogen containing heterocyclic ring containing one or two nitrogen atoms;
R^3 is selected from C_{1-10} alkyl, C_{3-8} cycloalkyl, phenyl-C_{1-6} alkyl, phenyl or a 4, 5, 6 or 7-membered monocyclic nitrogen containing heterocyclic ring containing one or two nitrogen atoms wherein the nitrogen containing heterocyclic ring is either unsubstituted or substituted with R^5 and R^6;
R^4 is C_{1-10} alkyl;

R^5 and R^6 are each independently selected from CO_2R^4, COR^4 or C_{1-10} alkyl.

In one embodiment of this aspect of the invention is the compound of the formula



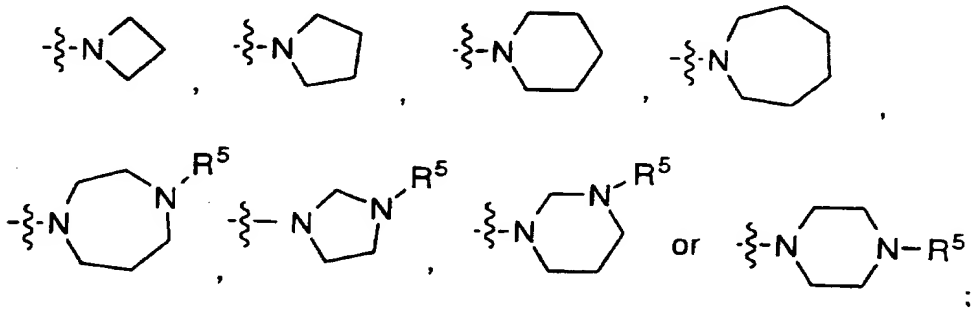
where all variables are as described above.

In a class of this aspect of the invention is the compound wherein

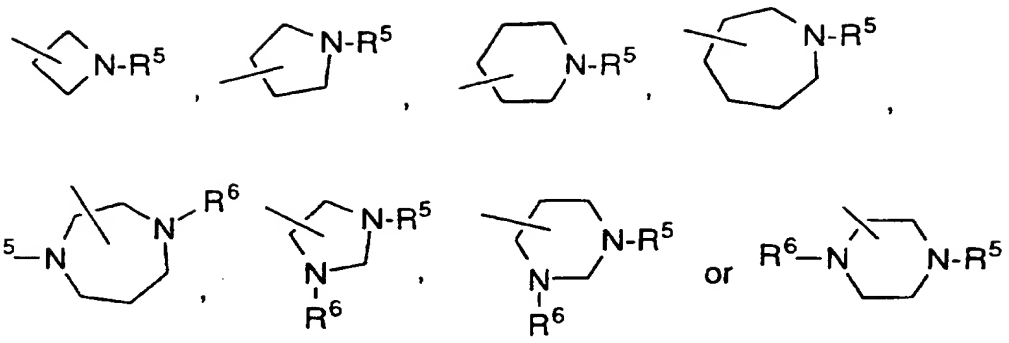
Y is selected from CN, CO_2H, CO_2CH_3, or $CO_2C(CH_3)_3$;

R^1 and R^2 are each independently selected from OR^3, SR^3, CN, $C{\equiv}CR^4$,

or a heterocyclic ring selected from

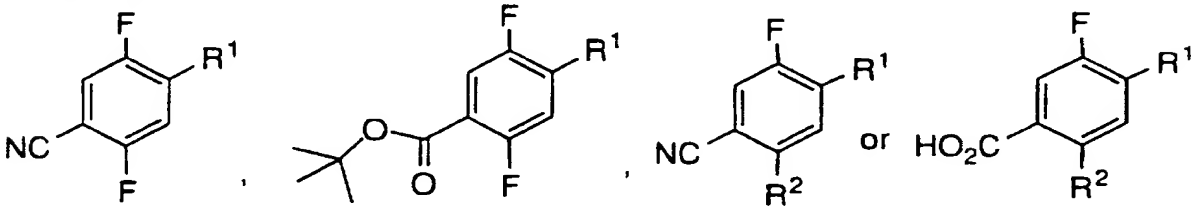


R^3 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, benzyl, phenyl or a heterocyclic ring selected from

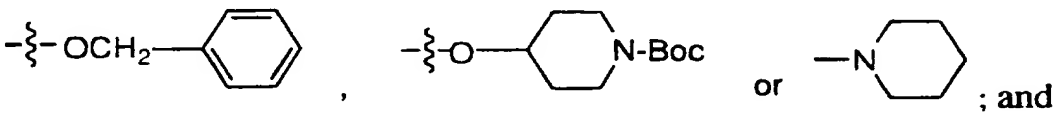


R^4 is C_{1-6} alkyl;
R^5 and R^6 are each independently selected from CO_2R^4, COR^4 or C_{1-6} alkyl.

In a subclass of this aspect of the invention is the compound of the formula

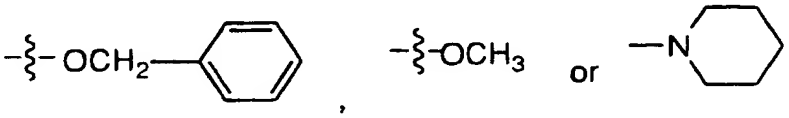


wherein R^1 is selected from

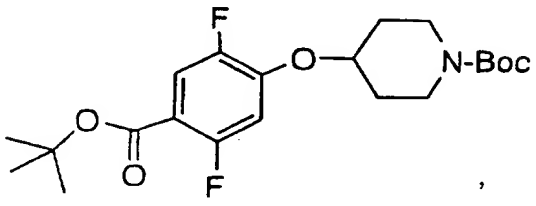


; and

R^2 is selected from



An illustration of this aspect of the invention is the compound selected from



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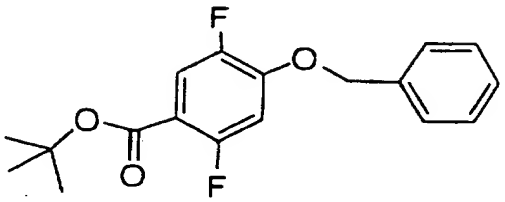

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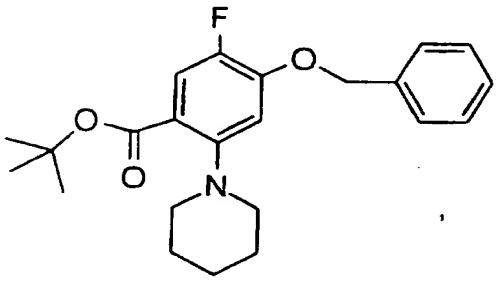

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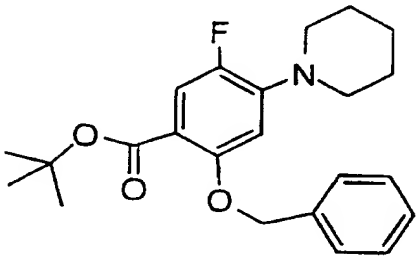

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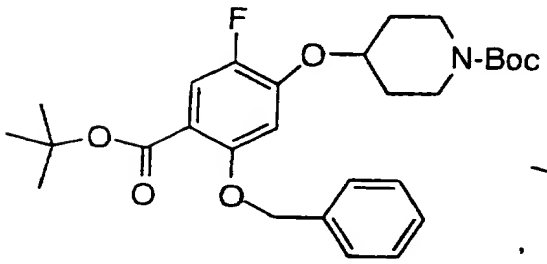

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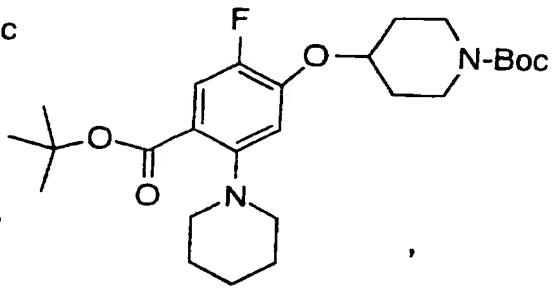

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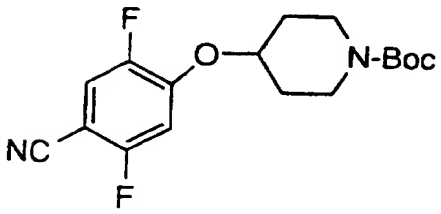

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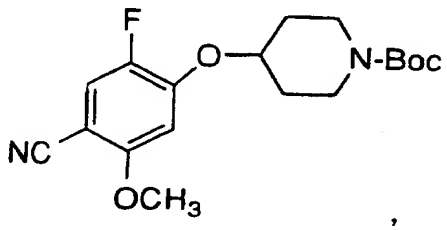

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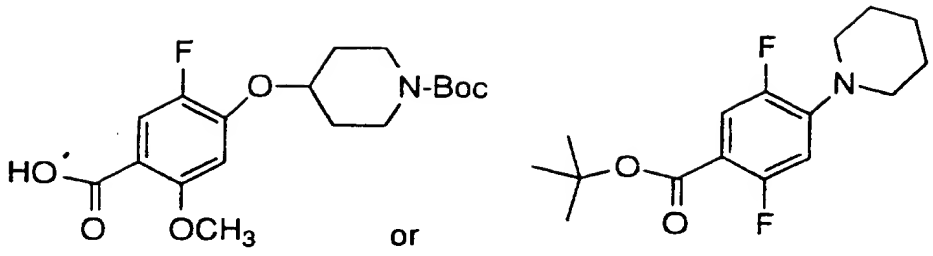


BRIEF DESCRIPTION OF THE DRAWINGS

Not Applicable

DETAILED DESCRIPTION OF THE INVENTION

The instant invention provides a process for regioselective nucleophilic substitution of trifluorobenzoate and/or trifluoronitrile. In a preferred embodiment of the present invention, 2,4,5-trifluorobenzoate/trifluorobenzonitrile is regioselectively substituted at the 4-position by a nucleophile to afford the 2,5-difluorobenzoate/difluorobenzonitrile in high yields. Preferably, the nucleophile is an oxygen nucleophile (e.g., alkoxide), a nitrogen heterocycle (e.g., piperidine), a sulfur nucleophile (e.g., thiol) or a carbon nucleophile (e.g., nitrile, acetylene). Additionally, the resultant 2,5-difluorobenzoate/difluorobenzonitrile can be subsequently substituted at the 2-position by a second nucleophile to afford the 5-fluorobenzoate/fluorobenzonitrile which is useful as an intermediate in the synthesis of fluorinated oxytocin antagonists, e.g., Compound A.

The nucleophilic substitution of trifluorobenzoate/trifluorobenzonitrile to form the difluorobenzoate/ difluorobenzonitrile can be run at a temperature range of -78 to 5°C, preferably, -78 to -30°C, most preferably, about -65°C. Subsequent substitution of the difluorobenzoate/difluorobenzonitrile with a nucleophile to form the monofluorobenzoate/monofluorobenzonitrile can be run at a temperature range of -50 to 50°C, preferably, 20 to 25°C, most preferably, about 5°C.

A variety of solvents can be utilized in the nucleophilic substitution reactions of the present invention. More specifically, the nucleophilic substitution reactions of the present invention can be run in a solvent selected from a hydrocarbon solvent (e.g., hexane, cyclohexane) an aromatic solvent (e.g., toluene, benzene) or an oxygenated organic solvent (e.g., DMF, NMP, an ether). Examples of ethers which are suitable for use in the present invention include, but are not limited to, diethyl ether, tert-butyl methyl ether, and tetrahydrofuran. Preferably, an oxygenated organic solvent is utilized. Most preferably, the reaction is run using THF, DMF or NMP as the solvent.

Abbreviations used in the instant specification are as follows:

AcOH or HOAc	=	acetic acid
Bn	=	benzyl
Boc or BOC	=	tert-butyloxycarbonyl
DCM	=	dichloromethane
DEAD	=	diethyl azodicarboxylate
DIEA	=	diisopropylethylamine
DMF	=	N, N-dimethylformamide
DMSO	=	dimethylsulfoxide
EDC	=	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et	=	ethyl
EtOAc	=	ethyl acetate
EtOH	=	ethanol
eq.	=	equivalent
FAB MS	=	fast atom bombardment mass spectroscopy
Me	=	methyl
MeOH	=	methanol
MTBE	=	tert-butyl methyl ether
NMP	=	1-methyl-2-pyrrolidinone
Ph	=	phenyl
r.t.	=	room temperature
THF	=	tetrahydrofuran

The compounds of the present invention, may have chiral centers and occur as racemates, racemic mixtures and as individual diastereomers, or enantiomers with all isomeric forms being included in the present invention. Therefore, where a compound is chiral, the separate enantiomers, substantially free of the other, are included within the scope of the invention; further included are all mixtures of the two enantiomers. Also included within the scope of the invention are polymorphs and hydrates of the compounds of the instant invention.

The term "preterm labor" shall mean expulsion from the uterus of a viable infant before the normal end of gestation, or more particularly, onset of labor with effacement and dilation of the cervix before the 37th week of gestation. It may or may not be associated with vaginal bleeding or rupture of the membranes.

The term "dysmenorrhea" shall mean painful menstruation.

The term "cesarean delivery" shall mean incision through the abdominal and uterine walls for delivery of a fetus.

The term "alkyl," as used herein, includes both straight and branched chain alkanes of the number of carbon atoms specified (e.g., C_{1-8} alkyl), or any number within this range (i.e., methyl, ethyl, 1-propyl, 2-propyl, n-butyl, s-butyl, t-butyl, etc.).

The term "cycloalkyl" shall mean cyclic rings of alkanes of three to eight total carbon atoms (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl).

The term "alkoxy," as used herein, refers to straight or branched chain alkoxides of the number of carbon atoms specified (e.g., C_{1-5} alkoxy), or any number within this range (i.e., methoxy, ethoxy, etc.).

The term "phenyl-C_{1-6} alkyl" refers to a phenyl ring attached to a C_{1-6} alkyl group, e.g., benzyl, phenylethyl, phenylpropyl, etc.

As used herein, the term "halogen" shall include, iodine, bromine, chlorine and fluorine.

The term "nitrogen heterocycle," as used herein, represents an unsubstituted or substituted stable 4- to 7-membered monocyclic

saturated ring system which consists of carbon atoms and from one to two nitrogen heteroatoms; the heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such nitrogen heterocycles include, but is not limited to, piperidinyl, piperazinyl, azepinyl, pyrrolyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl.

The term "oxygen nucleophile," as used herein, refers to an electron pair donor resided on an oxygen atom.

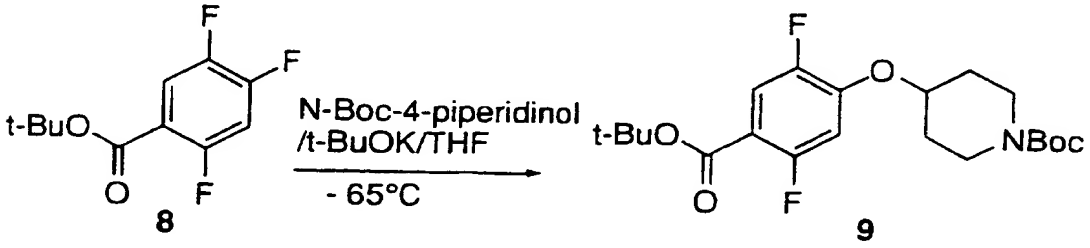
The term "sulfur nucleophile," as used herein, refers to an electron pair donor resided on a sulfur atom.

The term "carbon nucleophile," as used herein, refers to an electron pair donor resided on an carbon atom.

The following examples are provided to further define the invention without, however, limiting the invention to the particulars of these examples. For the compounds of Examples 1-14, which follow, ^{1}H NMR spectra were measured at 300 MHz on a Bruker AM-300 instrument, and ^{13}C NMR spectra were run at 75.5 MHz on the same instrument. ^{1}H and ^{13}C NMR spectras for the compounds of Examples 1-14 were consistent with structures.

EXAMPLE 1

Synthesis of Difluoroester **9** from Trifluoroester **8**

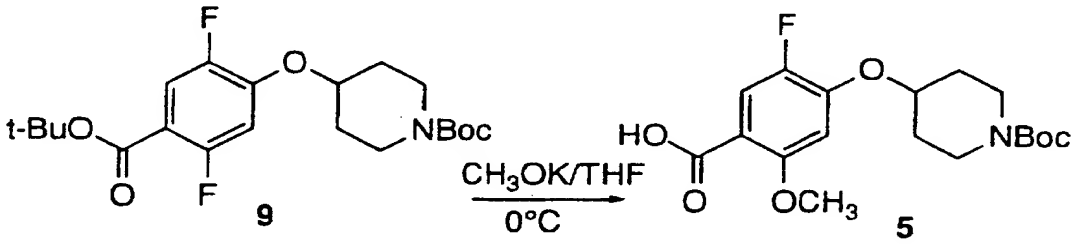


To a solution of N-Boc-4-piperidinol (1.95 g, 9.68 mmol) in THF (5.0 ml) was added a solution of t-BuOK in THF (Aldrich, 1.0 M, 10.6 ml) at 0°C and the resulting reaction mixture was stirred for 0.5 h at that temperature. The reaction mixture was slowly cannulated to a cold solution of trifluoroester **8** (2.05 g, 8.80 mmol) in THF (5.0

ml) at -65°C and was then aged at -30°C for 1.5 h. The reaction was quenched with water (5.0 ml) at -30°C and then extracted with MTBE (150 ml). The organic layer was washed with water (30 ml), then brine (30.0 ml) and dried over $MgSO_4$. Evaporation of the solvents gave an oily residue. Chromatography of the residue on silica gel (eluted with 5% ethyl acetate/hexane) provided 2.31 g of the desired product **9** (63.6% yield).

EXAMPLE 2

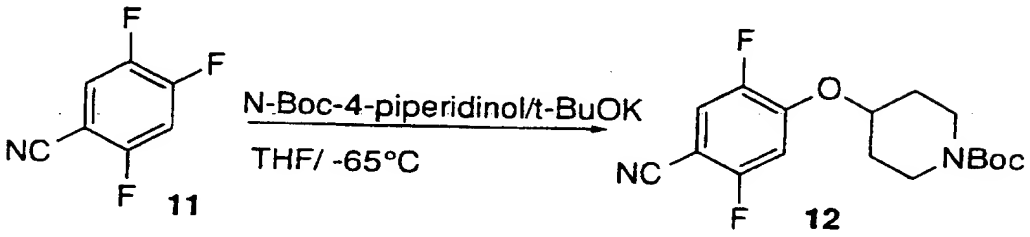
Synthesis of Monofluoroacid **5**



To a solution of t-BuOK in THF (1.0 M, 2.0 ml) was added MeOH (0.081 ml, 2.0 mmol) at -4°C and the resulting solution was stirred for 0.5 h. A THF solution of **9** (165 mg, 0.40 mmol) was introduced at -4°C and the reaction mixture was stirred at 0°C for 1.0 h. The reaction mixture was allowed to warm to 25°C and stirred for 6 h. The reaction mixture was diluted with MTBE (25 ml) and water (25 ml) at 25°C. The aqueous layer was separated and then neutralized with 2 N HCl to pH = 1. The neutralized aqueous layer was extracted with CH_2Cl_2 (25 ml x 2). The combined organic layers were washed with water (25 ml) and dried over $MgSO_4$. Evaporation of the solvent gave the solid acid **5**.

EXAMPLE 3

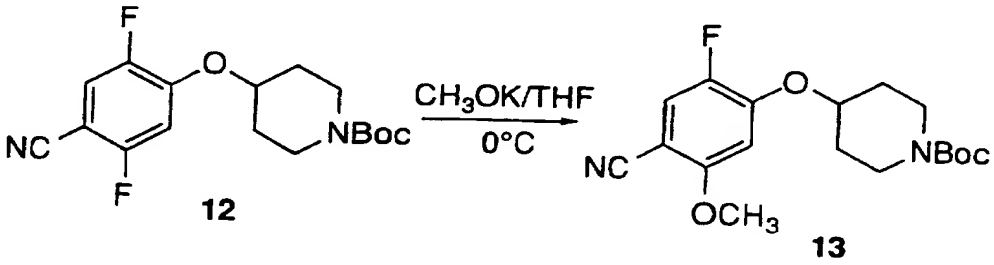
Synthesis of Difluoronitrile **12** from Trifluoronitrile **11**



A t-BuOK solution (1.0 M, 5.0 ml) was slowly added to a solution of N-Boc-4-piperidinol (1.0 g, 4.97 mmol) in THF (3.0 ml) at 5°C and the resulting mixture stirred for 0.5 h. The mixture was then transferred to a cold solution of trifluoronitrile **11** (Aldrich, 0.569 ml, 4.97 mmol) in THF (3.0 ml) at -65°C. The reaction mixture was stirred at -65°C for 3.0 h and then allowed to warm to 25°C over 1.0 h. The reaction mixture was quenched with water (25 ml) and was diluted with MTBE (100 ml). The organic layer was separated and washed with water (35 ml), brine (35 ml), and dried over $MgSO_4$. Evaporation of the solvent under vacuum provided 1.65 g of a white solid **12** (99% yield).

EXAMPLE 4

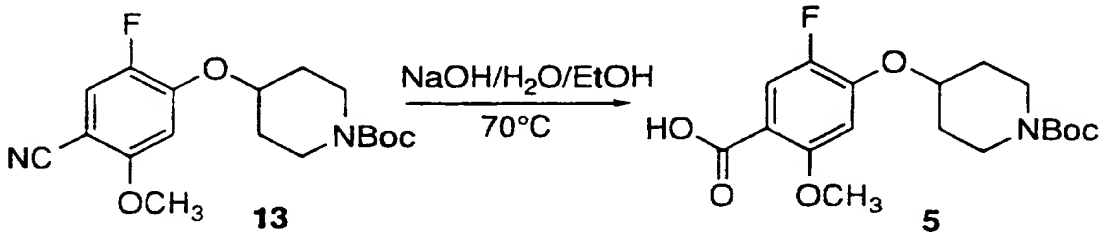
Synthesis of Monofluoronitrile **13** from Difluoronitrile **12**



MeOH (0.151 ml, 3.73 mmol) was added to a solution of t-BuOK in THF (1.0 M, 3.73 ml) at 5°C resulting in a light suspension which was stirred for 0.5 h at 5°C. The light suspension was cannulated into a cold solution of difluoronitrile **12** (0.84 g, 2.485 mmol) in THF (3.0 ml) at -50°C and then aged for 1.0 h at -50°C. The reaction mixture was warmed to 5°C over 0.5 h and stirred at 5°C for 2 h after which the reaction was quenched with water (15 ml). The reaction mixture was diluted with MTBE (100 ml), and the organic layer was washed with water (35 ml), then brine (35 ml). After drying over $MgSO_4$, the organic layer was evaporated to dryness to provide a waxy solid of monofluoronitrile **13** (0.83 g, 95% yield).

EXAMPLE 5

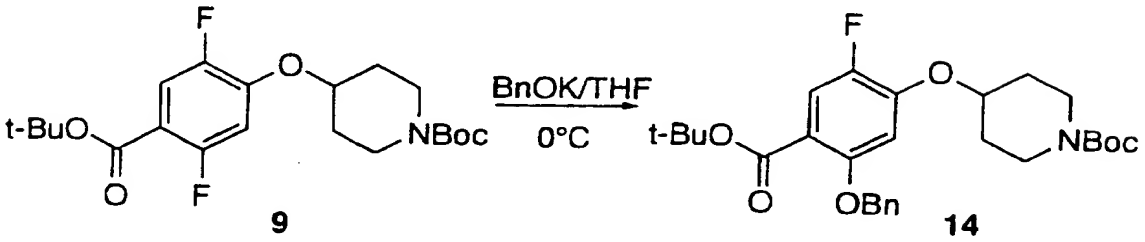
Synthesis of Monofluoroacid **5** from Monofluoronitrile **13**



A NaOH solution (3.0 ml, 50 wt %) was added to a solution of **13** (0.416 g, 1.19 mmol) in EtOH (3.0 ml), followed by addition of water (3.0 ml) at 25°C. The resulting slurry was heated to 70°C for 16 h and then cooled to 5°C. Conc. HCl was added at 5°C to adjust the pH to 1, and the mixture was then extracted with ethyl acetate (100 ml). The organic layer was separated and washed with water (25 ml), brine (25 ml) and dried over $MgSO_4$. Evaporation of the solvent gave the acid **5** as a white solid (0.40 g, 90% yield).

EXAMPLE 6

Synthesis of Monofluoroester **14** from Difluoroester **9**

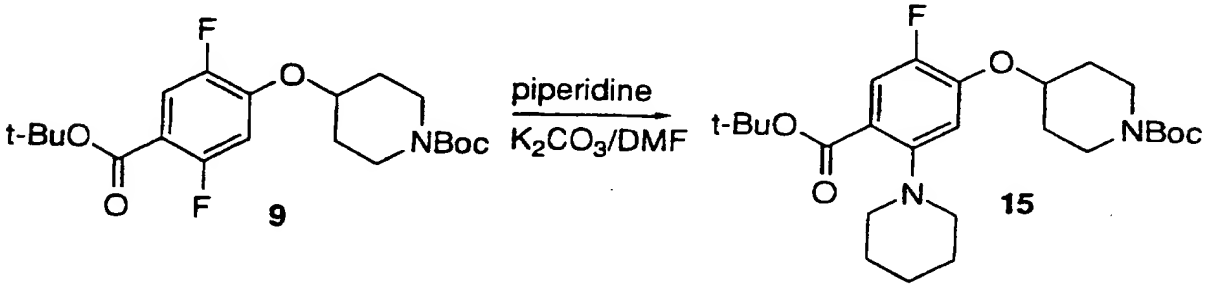


9 **14**

A solution of t-BuOK in THF (1.0 M, 0.55 ml) was added to a solution of benzyl alcohol (0.057 ml, 0.55 mmol) in THF (2.0 ml) at 5°C and the resulting mixture stirred at 5°C for 0.5 h. The difluoroester **9** (206 mg, 0.5 mmol) was introduced as a solid at 5°C and the reaction was stirred at 5°C for 4.5 h. The reaction was warmed to 25°C and stirred for an additional 1.5 h, then quenched with water (5.0 ml) and extracted with MTBE (50 ml). The organic layer was washed with water (15 ml), brine (15 ml) and dried over $MgSO_4$. Evaporation of the solvent afforded the desired product **14**.

EXAMPLE 7

Synthesis of Monofluoroester **15** from Difluoroester **9**

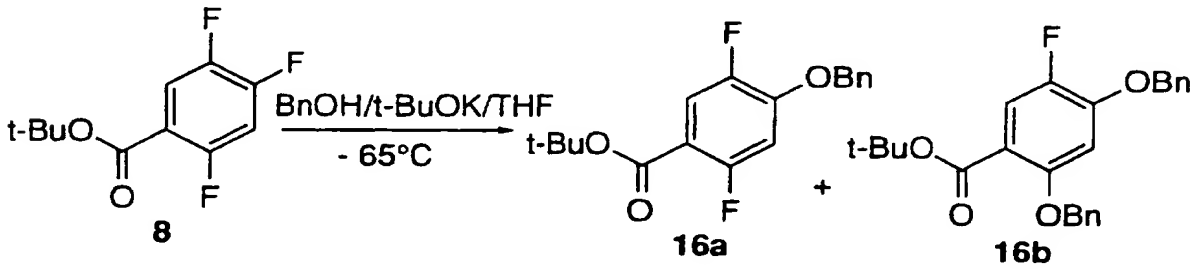


9 **15**

The starting material **9** (191 mg, 0.46 mmol), piperidine (0.0686 ml, 0.695 mmol) and potassium carbonate (128 mg, 0.928 mmol) were mixed together in DMF (5.0 ml) at 25°C. The slurry was stirred and heated to 110°C for 12 h. After cooling to 25°C, the reaction mixture was diluted with water (15 ml) and extracted with MTBE (100 ml). The organic layer was separated and washed with water (25 ml x 2), sat. $NaHCO_3$ (20 ml) and brine (20 ml). The organic layer was dried over $MgSO_4$ and evaporated to dryness. Chromatography of the residue on silica gel and elution with 15% ethyl acetate/hexane provided **15** in 75% yield (160 mg).

EXAMPLE 8

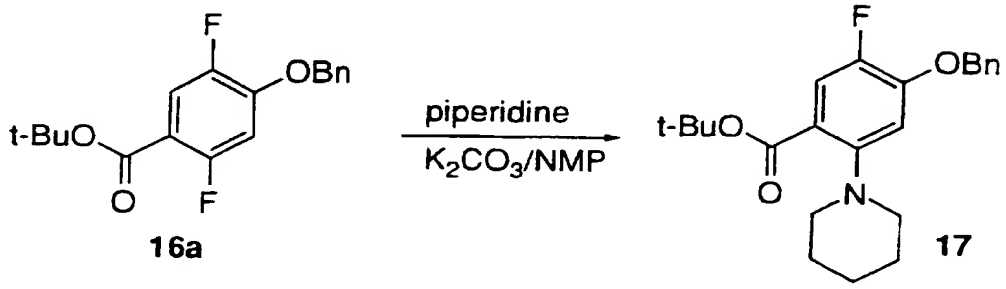
Synthesis of Difluoroesters **16a** and **16b** from Trifluoroester **8**



A solution of t-BuOK in THF (1.0 M, 1.06 ml) was added to a solution of benzyl alcohol (0.11 ml, 1.06 mmol) in THF (2.0 ml) at 5°C and the resulting mixture stirred at 5°C for 0.5 h. A solution of **8** (205.4 mg, 0.88 mmol) in THF (2.0 ml) was introduced slowly at 5°C and kept at 5°C for 3.5 h. The reaction was warmed to 25°C for 0.5 h, and then the reaction was quenched with water and diluted with MTBE (100 ml). The organic layer was separated and washed with water (25 ml) and brine (25 ml), followed by drying over $MgSO_4$. Evaporation of the solvent gave a residue which was chromatographed on silica gel. Elution with 5% ethyl acetate/hexane gave a first fraction containing difluoroester **16a** (114 mg, 40.5% yield) and a second fraction containing monofluoroester **16b** (107 mg, 29.8% yield).

EXAMPLE 9

Synthesis of Monofluoroester **17** from Difluoroester **16a**

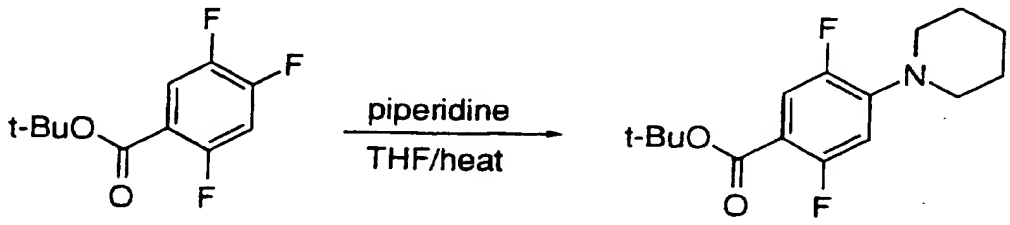


16a **17**

Piperidine (0.077 ml, 0.78 mmol) was added to a solution of difluoroester **16a** (100 mg, 0.31 mmol) in THF (2.0 ml) at 25°C, followed by addition of K_2CO_3 (86 mg, 0.62 mmol). The resulting suspension was stirred at 25°C for 2.0 h and then heated to reflux for 2.0 h. To this slurry was added NMP (2.0 ml) and refluxing continued for 12 h. The reaction mixture was diluted with water (10 ml) and extracted with MTBE (100 ml). The organic layer was separated and washed with water (25 ml x 2), sat. $NaHCO_3$ (25 ml) and brine (25 ml). After drying over $MgSO_4$, the solvent was removed under vacuum to give the product **17**.

EXAMPLE 10

Synthesis of Difluoroester **18** from Trifluoroester **8**

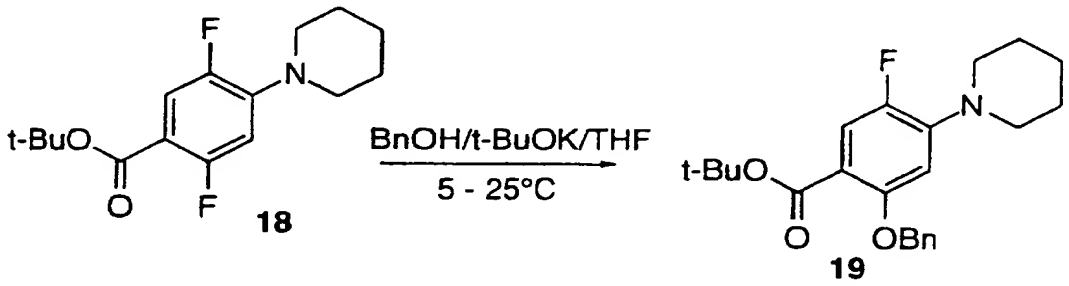


8 **18**

Piperidine (0.80 ml, 8.09 mmol) was added to a solution of trifluoroester **8** (0.84 g, 3.61 mmol) in THF (5.0 ml) at 25°C and the reaction mixture stirred for 1.0 h. The mixture was heated to reflux for 2 h, and then cooled to 25°C. The reaction mixture was diluted with water (35 ml) and extracted with MTBE (150 ml). The organic layer was washed with sat. $NaHCO_3$ (35 ml), brine (35 ml) and dried over $MgSO_4$. Evaporation of the solvent gave the desired product **18** as an oil (1.04 g, 96.7% yield).

EXAMPLE 11

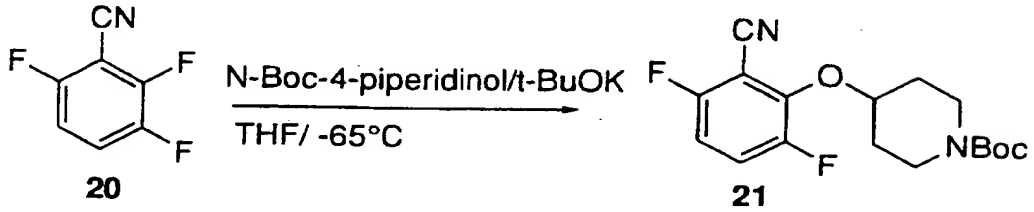
Synthesis of Monofluoroester **19** from Difluoroester **18**



Benzyl alcohol (0.187 ml, 1.81 mmol) was added to a solution of t-BuOK in THF (1.0 M, 1.81 ml) at 5°C and the resulting solution stirred for 0.5 h at that temperature. To this solution was added a solution of difluoroester **18** (538 mg, 1.81 mmol) in THF (2.0 ml) at 5°C over 10 min. The resulting solution was kept at 5°C for 1.5 h, then warmed to 25°C, and stirring continued for 2.0 h. The reaction was quenched with water (5.0 ml) at 25°C and extracted with MTBE (150 ml). The organic layer was washed with water (25 ml) and brine (25 ml). After drying over $MgSO_4$, the solvent was evaporated to give a residue which was chromatographed on silica gel and eluted with 10% ethyl acetate/hexane. Concentration of the appropriate fractions gave the desired product **19** which was obtained as an oil (0.5 g, 70.4% yield).

EXAMPLE 12

Synthesis of Difluoronitrile **21** from Trifluoronitrile **20**

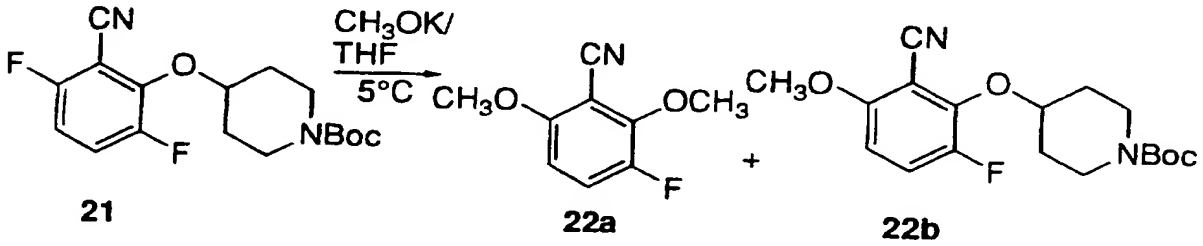


20 **21**

A solution of t-BuOK in THF (1.0 M, 3.18 ml) was added to a solution of N-Boc-4-piperidinol (0.64 g, 3.18 mmol) in THF (2.0 ml) at 5°C and the resulting solution stirred for 0.5 h at 5°C. The resulting solution was then slowly cannulated to a solution of trifluoronitrile **20** (Aldrich, 0.364 ml, 3.18 mmol) in THF (2.0 ml) at -65°C. The reaction was stirred at -65°C for 3.0 h. Water (5.0 ml) was added to quench the reaction at -65°C and then the mixture was warmed to 25°C and extracted with MTBE (150 ml). The organic layer was separated and washed with water (25 ml) and brine (25 ml). After drying over $MgSO_4$, the solvent was removed under vacuum to provide the product **21** as a white solid which was used, without further purification, in the next step.

EXAMPLE 13

Synthesis of Monofluoronitrile **22b** from Difluoronitrile **21**

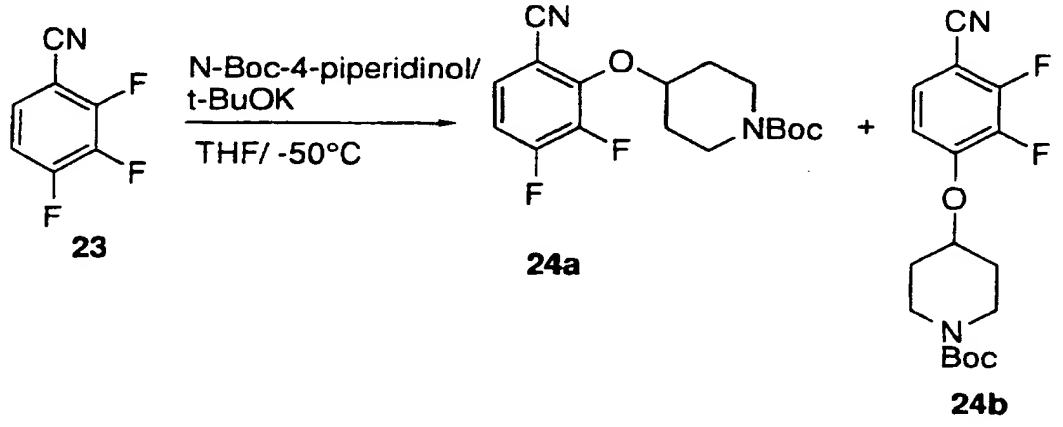


21 **22a** **22b**

MeOH (0.258 ml, 6.36 mmol) was added to a solution of t-BuOK in THF (1.0 M, 6.36 ml) at 5°C and the resulting light slurry was stirred at 5°C for 0.5 h. The slurry was slowly transferred to a cold solution of **21** (estimated: 3.18 mmol) in THF (4.0 ml) at -56°C and stirred at that temperature for 2 h. The reaction was warmed to 5°C and kept at that temperature for 4 h. The reaction was quenched with water (5.0 ml) at 5°C and extracted with MTBE (150 ml). The organic layer was washed with water (25 ml), brine (25 ml) and dried over $MgSO_4$. Evaporation of the solvent afforded a residue which was chromatographed on silica gel. Elution with 15% ethyl acetate/hexane gave a first fraction containing product **22a** and a second fraction containing the desired product **22b**.

EXAMPLE 14

Synthesis of Difluoronitrile **24** from Trifluoronitrile **23**



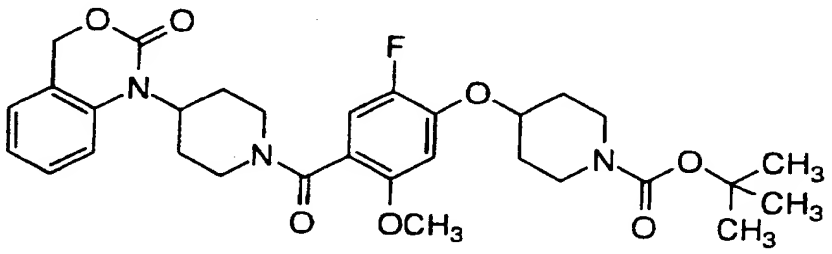
A solution of t-BuOK in THF (1.0 M, 6.30 ml) was added to a solution of N-Boc-4-piperidinol (1.23 g, 6.1 mmol) in THF (4.0 ml) at -40°C and the resulting solution stirred for 0.5 h at -40°C. The resulting solution was slowly cannulated to a solution of trifluoronitrile **23** (Aldrich, 0.364 ml, 3.18 mmol) in THF (4.0 ml) at -50°C. The reaction was stirred at -50°C for 0.5 h. Water (5.0 ml) was added to quench the reaction at -50°C and the reaction was then warmed to 25°C. The reaction mixture was extracted with MTBE (150 ml) and the

organic layer was separated, washed with water (25 ml) and dried over $MgSO_4$. The organic layer was evaporated to give a residue which was chromatographed on silica gel. Elution with 15% ethyl acetate/hexane gave a first fraction containing product **24a** (64%) and a second fraction containing product **24b** (14%).

Compound A was prepared from Monofluoroacid **5** according to Examples 15 to 17 which follow. For examples 15-17 which follow, ^1H NMR spectra were measured at 300 MHz on a Varian XL-300, at 400 MHz on a Varian XL-400, and at 360 MHz on a Nicolet NT-360 using $(CH_3)_4Si$ as an internal standard and Fast atom bombardment mass spectra (FAB MS) were obtained on a VG-ZAB-HF spectrometer. All NMRs for the compounds of Examples 15-17 which follow were consistent with structures.

EXAMPLE 15

1-(1-(4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1: 1-t-Butyloxycarbonyl-4-piperidinone (20 g, 0.10 mol), 2-aminobenzyl alcohol (13 g, 0.11 mol), and acetic acid (14 mL, 0.22 mol) were dissolved in dry toluene (500 mL). The solution was refluxed under inert atmosphere for 3 h with azeotropic removal of water. The solution was cooled to ambient temperature and concentrated under reduced pressure to one half of the original volume. To the solution was added $NaBH_3CN$ (20 g, 0.32 mol) and dry THF (300 mL). Acetic acid (10 mL, 0.15 mmol) was added dropwise over a period of about 1 h. The reaction was stirred at ambient temperature for 24 h.

The mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (750 mL). The EtOAc layer was washed with saturated aqueous $NaHCO_3$ (3x 500 mL) and brine (250 mL). The EtOAc layer was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography, using a gradient elution of 15-30% EtOAc-hexanes. 1-t-Butyloxycarbonyl-4-((2-hydroxymethyl)-phenylamino)piperidine was obtained as a gum (TLC: R_f = 0.30 (30:70 EtOAc:hexanes); HPLC(method A) retention time = 8.89 min).

Step 2: 1-t-Butyloxycarbonyl-4-((2-hydroxymethyl)-phenylamino)piperidine (24 g, 78 mmol) from Step 1 above was dissolved in dry THF (250 mL) and cooled to 0°C under an atmosphere of nitrogen. To the solution was added DIEA (41 mL, 0.24 mol) and triphosgene (8.54 g, 28.8 mmol). The reaction was stirred at 0°C for 1h, and then at ambient temperature for 24 h. Ether (250 mL) was added, the mixture was cooled to 0°C and then filtered to remove the hydrochloride salt of DIEA. The filtrate solvents were removed under reduced pressure and the residue was dissolved in EtOAc (750 mL). The EtOAc solution was washed with 5% aqueous citric acid (2x 500 mL), water (250 mL), and saturated aqueous $NaHCO_3$ (2x 500 mL). The EtOAc layer was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was boiled in ether (ca. 200 mL) until the solid had dissolved. Cooling overnight gave 1-(N-t-butyloxycarbonyl-4-piperidinyl)-4H-3,1-benzoxazin-2(1H)-one as off-white crystals, mp 143-145°C (TLC: R_f = 0.28 (30:70 EtOAc:hexanes); HPLC(method A) retention time = 8.77 min; FAB MS: m/z 333 ($M^+ + H$)).

Step 3: A stirred solution of 1-(N-t-butyloxycarbonyl-4-piperidinyl)-4H-3,1-benzoxazin-2(1H)-one (19 g, 57 mmol) from Step 2 above in EtOAc (500 mL) was cooled to 0°C. HCl gas was bubbled through the solution for 30 min. Stirring was continued at 0°C for 1 h, during which time a precipitate had formed, and the reaction was warmed to ambient temperature for 1 h. The stirred suspension was cooled to 0°C and cold ether (250 mL) was added. The precipitate was collected by filtration and washed with ether. The solid was dried under

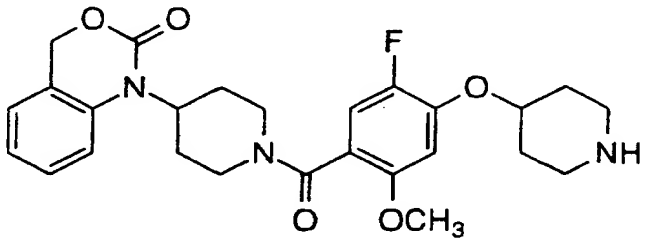
reduced pressure for 18 h, giving 1-(4-piperidinyl)-4H-3,1-benzoxazin-2(1H)-one hydrochloride as a white amorphous solid (TLC: R_f = 0.29 (90:10:1 CH_2Cl_2:MeOH:NH_4OH); HPLC(method A) retention time = 3.88 min; FAB MS: m/z 233 (M^+ + H)).

Step 4: To a solution of the hydrochloride salt of 1-(4-piperidinyl)-4(H)-3,1-benzoxazin-2(1H)-one (150 mg, 0.56 mmol) from Step 3 above in DMF (5 mL) was added 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-5-fluoro-2-methoxybenzoic acid, **5** (206 mg, 0.56 mmol), HOBT (92 mg, 0.60 mmol), and EDC (140 mg, 0.73 mmol). To the stirred solution was added DIEA (0.19 mL, 1.1 mmol) until the reaction was pH 7 as judged by spotting an aliquot on wetted E. Merck "colorpHast" pH 1-14 indicator strips. The reaction was stirred at ambient temperature for 18 h and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (50 mL) and washed with 5% aqueous citric acid (25 mL), water (25 mL), and saturated aqueous $NaHCO_3$ (25 mL). The EtOAc layer was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using a gradient elution of 1-3% MeOH-$CHCl_3$. The title compound, 1-(1-(4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one was obtained as an amorphous solid.

Analysis calculated for $C_{31}H_{38}FN_3O_7$, 0.2 EtOAc, 0.25 H_2O
C, 63.04; H, 6.67; N, 6.94
Found: C, 63.06; H, 6.56; N, 6.93
TLC: R_f = 0.17 (4:1 EtOAc:hexanes)
HPLC (method A) retention time = 9.8 min
FAB MS m/z 584 (M^+ + H)

EXAMPLE 16

1-(1-(4-(4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one

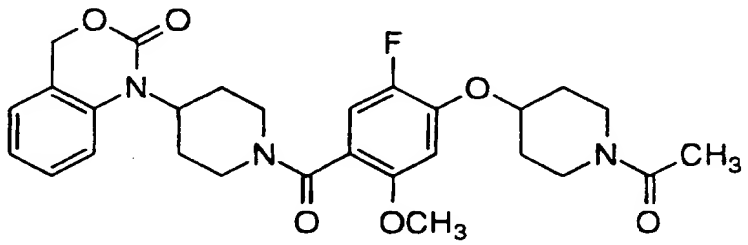


1-(1-(4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one from Example 15 was converted to the title compound using a procedure analogous to that given in Step 3 of Example 15. The hydrochloride salt of 1-(1-(4-(4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one was obtained as an amorphous solid.

Analysis calculated for $C_{26}H_{30}FN_3O_5$, 2.0 HCl, 0.15 EtOAc
C, 56.08; H, 5.87; N, 7.38
Found: C, 56.02; H, 5.94; N, 7.37
TLC: R_f = 0.12 (96:4:0.4 CH_2Cl_2:MeOH:NH_4OH)
HPLC(method A) retention time = 6.2 min
FAB MS m/z 484 (M^+ + H)

EXAMPLE 17

1-(1-(4-(N-acetyl-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one, Compound A



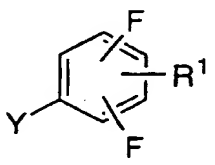
To a stirred solution of 1-(1-(4-(4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one of Example 16 (200 mg, 0.41 mmol) in DCM (5 mL) at ambient temperature was added acetic anhydride (77 mg, 0.75 mmol) and DIEA (0.17 mL, 1.0 mmol). The solution was stirred at ambient temperature for 24 h, diluted with DCM (20 mL), washed with saturated aqueous $NaHCO_3$ (50 mL), dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure and the residue was purified by pressurized silica gel column chromatography using a gradient elution of 2-5% MeOH-DCM. 1-(1-(4-(N-acetyl-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one was obtained as an amorphous solid.

Analysis calculated for $C_{28}H_{32}FN_3O_6$, 0.45 EtOAc, 0.65 H_2O
C, 62.03; H, 6.45; N, 7.28
Found: C, 62.02; H, 6.22; N, 7.26
TLC: R_f = 0.33 (97:3 CH_2Cl_2:MeOH)
HPLC (method A) retention time = 7.4 min
FAB MS m/z 526 ($M^+ + H$)

While the foregoing specification teaches the principles of the present invention, with examples for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

WHAT IS CLAIMED IS:

1. A compound of the formula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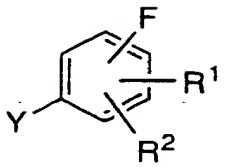
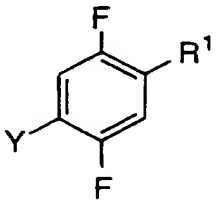


wherein Y is selected from CN, CO_2H or CO_2-C_{1-6} alkyl;
R^1 and R^2 are each independently selected from OR^3, SR^3, CN, $C{\equiv}CR^4$,
or a 4, 5, 6 or 7-membered monocyclic nitrogen containing heterocyclic ring containing one or two nitrogen atoms;
R^3 is selected from C_{1-10} alkyl, C_{3-8} cycloalkyl, phenyl-C_{1-6} alkyl, phenyl or a 4, 5, 6 or 7-membered monocyclic nitrogen containing heterocyclic ring containing one or two nitrogen atoms wherein the nitrogen containing heterocyclic ring is either unsubstituted or substituted with R^5 and R^6;
R^4 is C_{1-10} alkyl;
R^5 and R^6 are each independently selected from CO_2R^4, COR^4 or C_{1-10} alkyl.

2. The compound of Claim 1 of the formula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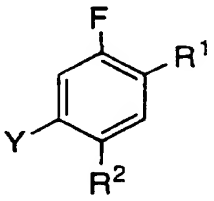
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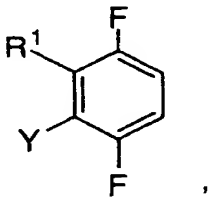
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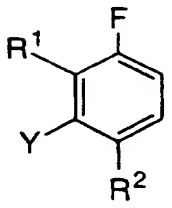
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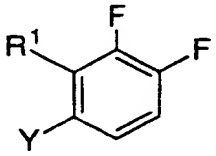
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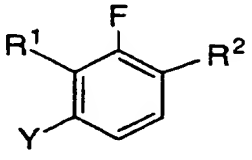
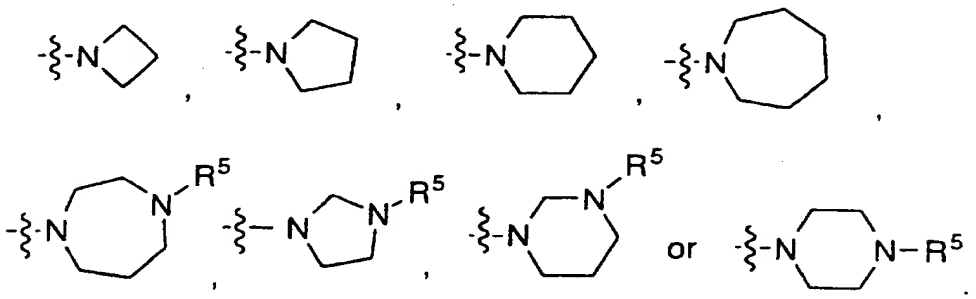
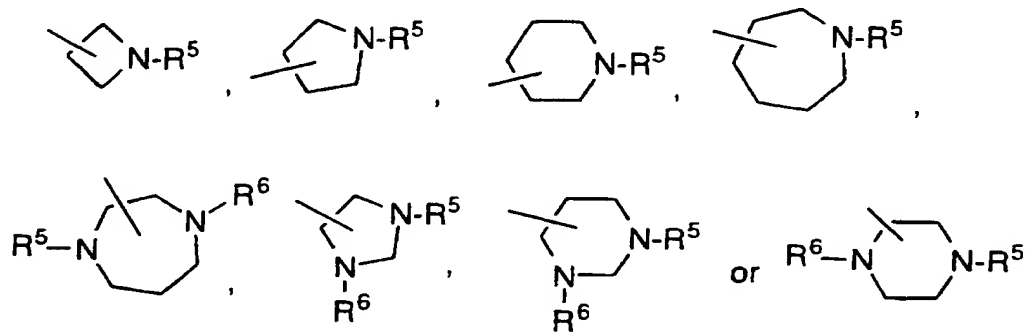


3. The compound of Claim 2, wherein
Y is selected from CN, CO_2H, CO_2CH_3, or $CO_2C(CH_3)_3$;
R^1 and R^2 are each independently selected from OR^3, SR^3, CN, $C{\equiv}CR^4$,
or a heterocyclic ring selected from

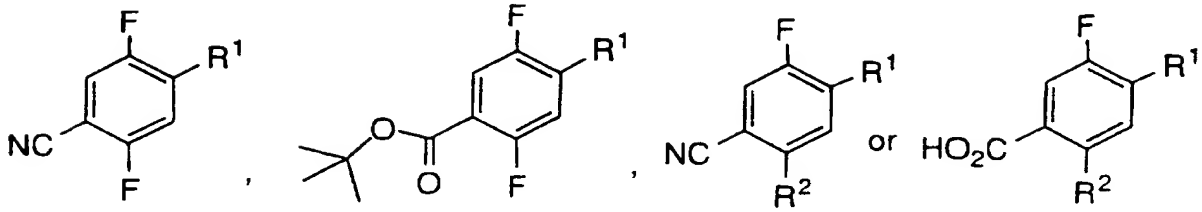


R^3 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, benzyl, phenyl or a heterocyclic ring selected from

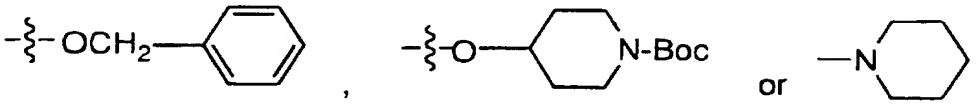


R^4 is C_{1-6} alkyl;
R^5 and R^6 are each independently selected from CO_2R^4, COR^4 or C_{1-6} alkyl.

4. The compound of Claim 3 of the formula

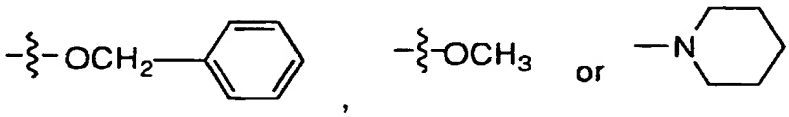


wherein R^1 is selected from

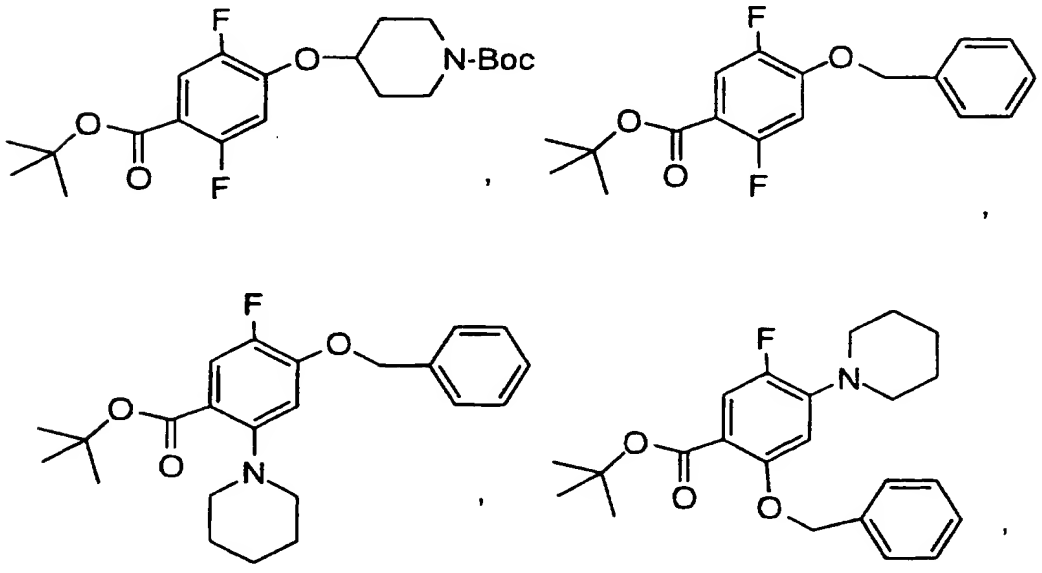


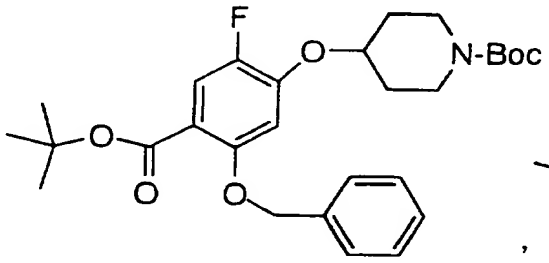
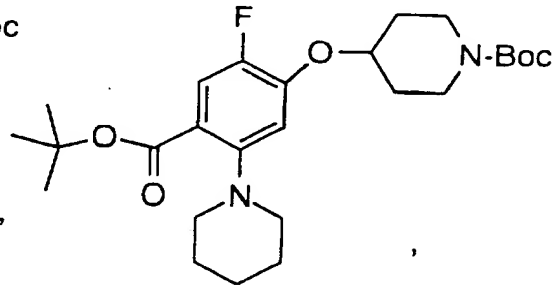
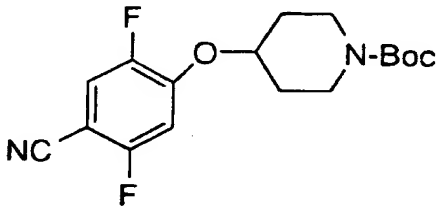
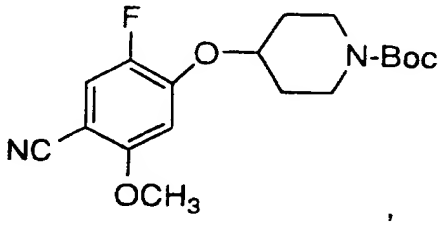
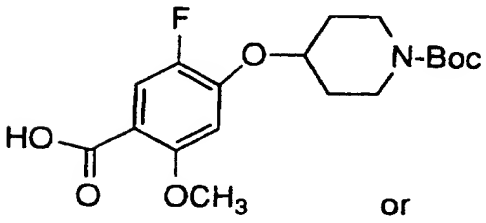
; and

R^2 is selected from



5. The compound of Claim 4, selected from

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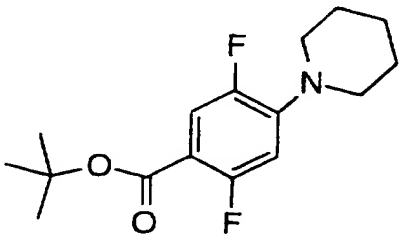
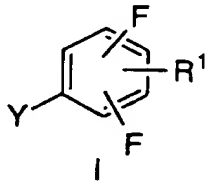
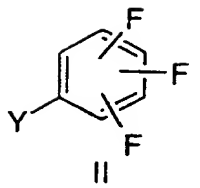


6. A process for forming a difluoro compound I



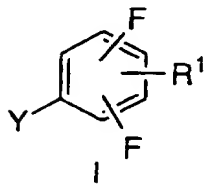
I

comprising reacting a trifluoro compound II



II

with a nucleophilic agent R^1 to obtain the difluoro compound I



I

wherein Y is selected from CN or CO_2-C_{1-6} alkyl;

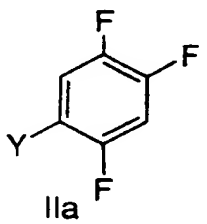
R^1 is selected from OR^3, SR^3, CN, $C{\equiv}CR^4$,
or a 4, 5, 6 or 7-membered monocyclic nitrogen containing heterocyclic ring containing one or two nitrogen atoms;

R^3 is selected from C_{1-10} alkyl, C_{3-8} cycloalkyl, phenyl-C_{1-6} alkyl, phenyl or a 4, 5, 6 or 7-membered monocyclic nitrogen containing heterocyclic ring containing one or two nitrogen atoms wherein the nitrogen containing heterocyclic ring is either unsubstituted or substituted with R^5 and R^6;

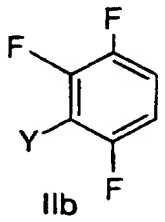
R^4 is C_{1-10} alkyl; and

R^5 and R^6 are each independently selected from CO_2R^4, COR^4 or C_{1-10} alkyl.

7. The process of Claim 6, wherein the trifluoro compound is selected from

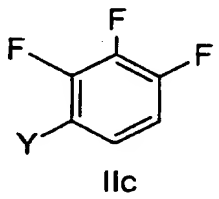


IIa



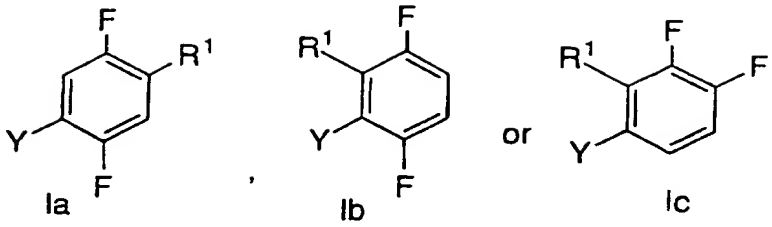
IIb

or

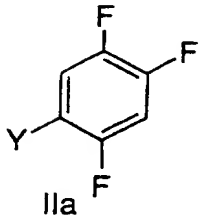


IIc

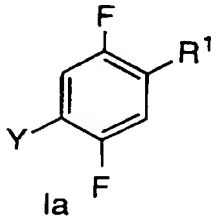
and the difluoro compound is selected from



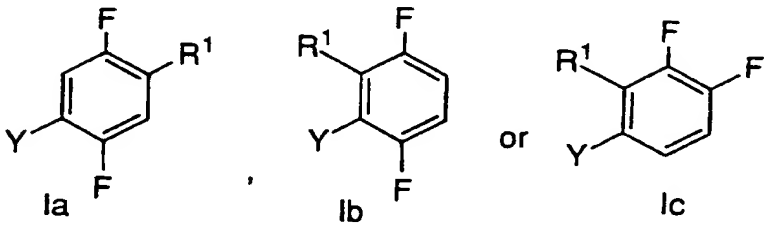
8. The process of Claim 7, wherein the trifluoro compound is



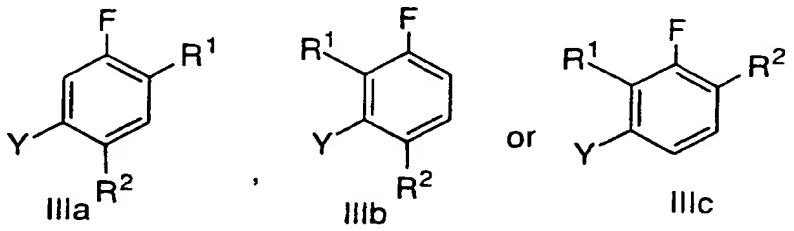
and the difluoro compound is



9. The process of Claim 7, further comprising the step of reacting the difluoro compound selected from

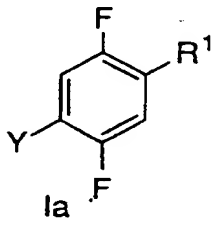


with a second nucleophilic agent R^2 to obtain a monofluoro compound selected from

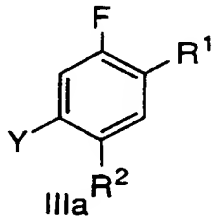


wherein R^2 is selected from OR^3, SR^3, CN, $C{\equiv}CR^4$, or a 4, 5, 6 or 7-membered monocyclic nitrogen containing heterocyclic ring containing one or two nitrogen atoms.

10. The process of Claim 9, wherein the difluoro compound is



and the monofluoro compound is



11. The process of Claim 6, wherein the reaction is run at a temperature range of about -78°C to about 5°C.

12. The process of Claim 11, wherein the reaction is run at a temperature range of about -78°C to about -30°C.

13. The process of Claim 12, wherein the reaction is run at a temperature of about -65°C.

14. The process of Claim 9, wherein the reaction of the difluoro compound with the second nucleophile is run at a temperature range of about -50°C to about 50°C.

15. The process of Claim 14, wherein the reaction of the difluoro compound with the second nucleophile is run at a temperature range of about -20°C to about 25°C.

16. The process of Claim 15, wherein the reaction of the difluoro compound with the second nucleophile is run at a temperature of about 5°C.

17. The process of Claim 6, wherein the reaction is run in a solvent selected from a hydrocarbon solvent, an aromatic solvent or an oxygenated organic solvent.

18. The process of Claim 17, wherein the solvent is an oxygenated organic solvent.

19. The process of Claim 18, wherein the solvent is selected from THF, DMF or NMP.

20. The process of Claim 9, wherein the reaction is run in a solvent selected from a hydrocarbon solvent, an aromatic solvent or an oxygenated organic solvent.

21. The process of Claim 20, wherein the solvent is an oxygenated organic solvent.

22. The process of Claim 21, wherein the solvent is selected from THF, DMF or NMP.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/02877

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :C07C 255/33, 255/35, 255/49
US CL :558/415, 416, 419, 423
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 558/415, 416, 419, 423

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,332,851 A (KUMAI et al.) 26 July 1994, see entire document, especially column 2, lines 20-54.	1-22 (in part)
X	US 4,684,734 A (KAIEDA et al.) 04 August 1987, see entire document, especially columns 9 and 10.	1-22 (in part)

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
06 MAY 1997

Date of mailing of the international search report
11 JUL 1997

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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/02877

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-22 (in part)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.